UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,233	10/24/2003	Zehra Kaymakcalan	BBI-190RCE	1420

959 7590 03/04/2008

LAHIVE & COCKFIELD, LLP
ONE POST OFFICE SQUARE
BOSTON, MA 02109-2127

EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
03/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,233	KAYMAKCALAN ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17,21-24,31,34,35,40-45,48,49,52 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

   Applicant's submission filed on November 8, 2007 has been entered.

   Claims 1-14, 18-20, 25-30, 32, 33, 36-39, 46, 47, 50 and 51 have been canceled.

   Claims 15, 21, 42, 48, 52 and 53 have been amended.

   Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 are pending.

   Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 are under consideration as they read on a method for treating arthritis by administering an anti-TNFα antibody, wherein the species of arthritis is "rheumatoid arthritis" is acknowledged.

2. The rejections of record can be found in the previous Office Action, mailed August 8, 2007.

   The previous rejection under 35 U.S.C. § 112, 2nd paragraph, has been withdrawn in view of applicant's amendment.

   The previous rejection under 35 U.S.C. § 112, 1st paragraph, has been withdrawn upon further consideration.

   New Grounds of Rejection are put forth below

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating arthritis with 0.1 mg/kg of any anti-TNFα antibody or for treating arthritis with 0.1 mg/kg of any anti-TNFα antibody wherein said arthritis is treated by alleviating the symptom vascularity or for treating arthritis with 0.1 mg/kg of the D2E7 anti-TNFα antibody or an anti-TNFα antibody having the properties recited in claim 41, wherein arthritis is treated by alleviating the symptoms from the group consisting of bone erosion, cartilage erosion and inflammation, *does not reasonably provide enablement for* treating arthritis with 0.01-0.1

mg/kg of any anti-TNFα antibody or for treating arthritis with 0.01-0.1 mg/kg of any anti-TNFα antibody wherein arthritis is treated by alleviating the symptoms from the group consisting of bone erosion, cartilage erosion, inflammation, and vascularity or for treating arthritis with 0.1 mg/kg of the infliximab anti-TNFα antibody wherein arthritis is treated by alleviating the symptoms from the group consisting of bone erosion, cartilage erosion and inflammation.

This is a New Grounds of Rejection.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant argues that the claims are enabled with a focus on the data displayed in Figure 4, emphasizing that the data presented in this figure shows a beneficial effect for at least one mouse even at the low dose of 0.01 mg/kg for both D2E7 and infliximab. Applicant further states, "[e]ven if, arguendo, some testing would be required to determine if the dose is affective on a particular patient, such experimentation would certainly not be 'undue' for a skilled artisan, since drug dosages have to be optimized for each patient regardless."

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed August 8, 2007, and as further put forth below.

As stated in the previous Office Action mailed August 8, 2007, the instant specification discloses the treatment of mice transgenic for TNFα (tg197 mice), which is one model system for rheumatoid arthritis, with two anti-TNFα antibodies, D2E7 and Remicade, including 0.01 mg/kg once per week for 10 weeks.

Neither D2E7 nor Remicade appear to show any consistent effect on arthritic scores when dosed at 0.01 mg/kg once per week for 10 weeks (see, in particular, Example 1, part B and Figures 1, 2 and 4).

Moreover, as a second measure of treatment efficacy, four histopathological features were measured at the end of the 10 week treatment. Again, neither D2E7 nor Remicade appear to be able to elicit an improvement in the measured histological features at the 0.01 mg/kg dose (see, in particular, Example 1, part D and Figure 5).

Furthermore, according to the data presented in Figure 5, while the D2E7 antibody does appear to be able to treat arthritis in the Tg197 mouse model with 0.1 mg/kg anti-TNFα antibody wherein arthritis is treated by alleviating the symptoms from the group consisting of bone erosion, cartilage erosion, inflammation, and vascularity, 0.1 mg/kg infliximab antibody is only able to treat arthritis in the Tg197 mouse model wherein arthritis is treated by alleviating the symptom vascularity.

MPEP § 2164.08 teaches that "[t]he focus of the examination inquiry is whether everything within the scope of the claim is enabled." However, applicant has not established that the skilled artisan could use a dose of as little as 0.01 mg/kg to treat rheumatoid arthritis in human patients given the data disclosed in the instant specification which demonstrates no consistent effect of treating tg197 mice with 0.01 mg/kg anti-TNFα antibody.

With respect to Figure 4, applicant argues that it "…indicates that a 0.01 mg/kg dose of Adalimumab resulted in an arthritic score as low as about 1.0 in at least one mouse (see low point of standard deviation mark) compared to the lowest arthritic score of about 2.25 in a control mouse. Similarly, a 0.01 mg/kg dose of Infliximab resulted in at least one mouse that had an arthritic score of about 1.75 compared to the lowest arthritic score in a control mouse of about 2.25. Applicants respectfully submit that these results indicate efficacy of both Adalimumab and Infliximab at a dosage of 0.01 mg/kg. Applicants respectfully submit that the effect on arthritic score need not affect each and every mouse in a study in order for the dose to be enabled and that it is particularly significant that at least one mouse in the study had an arthritic score of about 1.0, which is substantially and significantly lower than 2.25, the lowest arthritic score for a control mouse."

As a preliminary matter, in contrast to applicant's argument, based on the disclosure of the instant specification and objective evidence of record it is far from clear what the error bars shown in figure 4 represent.

On the one hand, applicant refers to the error bars shown in Figure 4 as a measure of "standard deviation" and yet the instant specification does not appear to disclose what they represent. To further complicate matters, the instant specification refers to the error bars of figure 1 as "standard error". While the instant specification does not define or further explain the meaning of "standard error" or "standard deviation" and how they relate one to the other, it seems they are different and do affect how the skilled artisan would understand the error bars of figure 4 (the examiner attaches herewith a reference describing in lay terms how the "standard error" and "standard deviation" differ, see http://www.graphpad.com/faq/viewfaq.cfm?faq=201, attached herewith).

Furthermore, in this regard it is noted that MPEP § 2164.06(c) states: "[a]rguments of counsel may be effective in establishing that an examiner has not properly met his or her burden or has otherwise erred in his or her position. However, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick,* 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement. See *In re Knowlton,* 500 F.2d at 572, 183 USPQ at 37; *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979).<"

That said, applicant's argument is further not convincing for several reasons.

Assuming for the sake of argument that applicant's assertion "0.01 mg/kg dose of Adalimumab resulted in an arthritic score as low as about 1.0 in at least one mouse…compared to the lowest arthritic score of about 2.25 in a control mouse…a 0.01 mg/kg dose of Infliximab resulted in at least one mouse that had an arthritic score of about 1.75 compared to the lowest arthritic score in a control mouse of about 2.25," is accurate the skilled artisan would still not be able to practice the full breadth of the claimed invention with any degree of predictability and in the absence of undue experimentation.

This is because a corollary of applicant's argument is that a 0.01 mg/kg dose of Adalimumab resulted in an arthritic score *as high as about 3.65* in at least one mouse…compared to the *highest arthritic score of about 2.85* in a control mouse…a 0.01 mg/kg dose of Infliximab resulted in at least one mouse that had an arthritic score *of about 3.75* compared to the *highest arthritic score in a control mouse of about 2.85*.

In other words, this is the equivalent of saying that in some cases the patient being treated with 0.01 mg/kg/week D2E7 or infliximab will improve compared to a patient who has never been treated and in other cases the patient will either not improve or be about 30% sicker than had they never been treated. Moreover, the instant specification provides no direction or guidance as to how the skilled artisan would go about predicting which patients are likely to benefit and which will either show no improvement or become significantly more ill than had they not been treated at all. Thus, to practice the claimed method to its full breadth the skilled artisan must suspend the credo first do no harm. The examiner submits that undue experimentation would be required of the skilled artisan to practice the claimed method to the extent of its breadth in any practical sense.

Furthermore, the examiner submits that Figure 4, upon which applicant's argument is based, displays the mean arthritic score as measured *at week 10* after 10 consecutive weeks of treatment for the D2E7 and infliximab (aka remicade) anti-TNFα antibodies. In contrast, Figures 1 and 2 display the mean arthritic scores as measured at *all weeks*, i.e., weeks 1, 2, 3, 4…and at week 10 for the D2E7 and infliximab antibodies, respectively. As shown in Figures 1, there were several weeks where the *group of mice* treated with D2E7 at 0.01 mg/kg had *greater mean arthritic scores* than the control group, a trend which is even more pronounced for infliximab in Figure 2. Thus, assuming for the sake of argument that the data applicant points to in Figure 4 were of actual statistical and practical significance, which has not yet been demonstrated, this would still not demonstrate a reasonable correlation between the scope of the claims and scope of enablement set forth because it represents the cumulative effect of 10 consecutive treatments and yet the claims are of far broader scope.

Thus, undue experimentation would be required to practice the claimed invention commensurate with the scope of the claims from the written disclosure alone. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In

view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Furthermore, regarding in vivo methods which rely on generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP also states that physiological activity can be considered inherently unpredictable.

In Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "[W]here there is "no indication that one skilled in [the] art would accept without question statements [as to the effects of the claimed drug products] and no evidence has been presented to demonstrate that the claimed products do have those effects," an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement" and "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 15-17 and 21-24 stand rejected under 35 U.S.C. 102(b) as anticipated by Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.), essentially for the reasons of record as put forth in the Office Action mailed August 8, 2007.

With respect to Stephens, Applicant argues (applicant's emphasis) "Stephens mentions a 0.01 mg/kg dose in the study and provides a general statement that '[a]ll patients who receive CDP571 scored a reduction in pain scale by week 1', all discussion of the data in support of that general statement are for 0.1mg/kg and 10 mg/kg. Stephens shows no data on the 0.01 mg/kg dose and does not discuss the effectiveness of this dose at all, nor is it tested further in

subsequent infusions, suggesting that it was ineffective in their study. Applicants respectfully submit that a skilled artisan would no doubt assume that this dose was not studied further because it was not effective. In addition, there was no indication or evidence that the 0.01 mg/kg dose 'treated arthritis' as required by Applicants' claims."

The examiner does not disagree with applicant's argument in so far as Stephens providing "a general statement that '[a]ll patients who receive CDP571 scored a reduction in pain scale by week 1', all discussion of the data in support of that general statement are for 0.1mg/kg and 10 mg/kg. Stephens shows no data on the 0.01 mg/kg dose and does not discuss the effectiveness of this dose at all,…in addition, there was no indication or evidence that the 0.01 mg/kg dose 'treated arthritis' as required by Applicants' claims."

However, the disclosure of Stephens is still sufficient to anticipate the instant claims essentially for the reasons of record.

As stated in the prior Office Action, Stephens teaches a method of treating rheumatoid arthritis comprising administering a single 0.1 mg/kg dose of humanized anti-TNFα antibody, CDP571. Stephens further teaches that the disease activity measures included tender and swollen joints, and that patients who received placebo did not improve whereas CDP571 had a dose-dependent effect on all patients treated (see entire document, in particular pages 326-327). Furthermore, all patients receiving CDP571 scored a reduction in pain scale by week 1 as taught by the following: "First infusion - *Patients who received placebo did not improve. In contrast, there was a dose-dependent effect of CDP571 treatment* with maximum patient responses after 10 mg/kg. After CDP571 10 mg/kg...*All patients who received CDP571 scored a reduction in pain scale by week 1*." See, Stephens, page 327, 1st paragraph, emphasis added.

Applicant further argues that (applicant's emphasis) "Stephens discloses only infusions of CDP571, not injections of an anti-TNFα antibody in a 0.01 mg/kg dose, which is required by Applicants' claims as amended."

Applicant's argument is not found convincing.

The instant specification does not explicitly distinguish an "injection" from an "infusion". For example, see the instant specification at page 17, 1st paragraph: "The compositions of this invention may be in a variety of forms suitable for low dose administration. These include, for example, liquid, semi-solid and solid dosage forms, *such as liquid solutions (e.g., injectable and infusible solutions),* dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of *injectable or infusible solutions*, such as compositions similar to those used for passive immunization of humans with other antibodies or other TNF.alpha. inhibitors. The preferred mode of administration is parenteral (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, a low dose of the antibody or other TNF.alpha.

inhibitor is *administered by intravenous infusion or injection*. In another preferred embodiment, a low dose of the antibody or other TNF.alpha. inhibitor is administered by intramuscular or subcutaneous injection." (emphasis added). Thus the relationship between these words is not made clear from the instant specification, i.e., are they synonyms, non-overlapping entities, or genus-species.

Looking at the definitions of these terms on the internet, they appear to be used in a genus-species way, i.e., an infusion refers to the slow administration of a drug via injection (see the compiled internet definitions of these terms according to Google, http://www.google.com/search?hl=en&rls=GGLD%2CGGLD%3A2004-30%2CGGLD%3Aen&q=define%3A+injection AND http://www.google.com/search?hl=en&rls=GGLD%2CGGLD%3A2004-30%2CGGLD%3Aen&q=define%3A+infusion attached herewith).

Thus, the terms "injection" and "infusion", given their broadest reasonable interpretation consistent with the instant specification and with the knowledge in the art appear to be related as genus to species.

Accordingly, in contrast to applicant's argument the *infusion* of 0.1 mg/kg anti-TNFα antibody into a rheumatoid arthritis patient as taught by Stephens anticipates *injection* of 0.1 mg/kg anti-TNFα antibody into a rheumatoid arthritis patient as claimed.

Thus, Stephens anticipates the instant claims.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 stand are rejected under 35 U.S.C. § 103(a) as unpatentable over Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.), in view of Salfeld et al. (US Patent No. 6,258,562) and den Broeder et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42).

Applicant argues the instant claims are non-obvious over the cited references because the references allegedly fall short in their teachings as combined, teach away from the claimed invention, and motivation to combine the cited references is lacking.

<u>The Stephens Reference</u>

Applicant argues the Stephens reference does not teach an injection regime, and that it teaches away "since Stephens provides no teaching that a 0.1 mg/kg dose of CDP571 is effective in treating arthritis and, moreover, teaches that a low dose of the antibody mounts an immune response and is cleared from the patient's system to a greater extent than a higher dose, e.g., 10 mg/kg, of CDP571." (see applicant's remarks, paragraph bridging pages 9-10).

With respect to the administration of 0.1 mg/kg anti-TNFα antibody to treat rheumatoid arthritis, as stated in the prior Office Action, Stephens teaches a method of treating rheumatoid arthritis comprising administering a single 0.1 mg/kg dose of humanized anti-TNFα antibody, CDP571. Stephens further teaches that the disease activity measures included tender and swollen joints, and that patients who received placebo did not improve whereas CDP571 had a dose-dependent effect on all patients treated (see entire document, in particular pages 326-327). Furthermore, all patients receiving CDP571 scored a reduction in pain scale by week 1 as taught by the following: "First infusion - *Patients who received placebo did not improve. In contrast, there was a dose-dependent effect of CDP571 treatment* with maximum patient responses after 10 mg/kg. After CDP571 10 mg/kg...*All patients who received CDP571 scored a reduction in pain scale by week 1*." See, Stephens, page 327, 1st paragraph, emphasis added.

Moreover, while Stephens does teach increased CPD571 clearance when patients are treated over particular time periods and at particular dosages, i.e., 8 weeks after a single administration of 0.1 mg/kg CDP571 anti-TNFα there is an increase in anti-CDP571 IgG production, and subsequent doses of CDP571 anti-TNFα antibody at 1 or 10 mg/kg resulted in increased CPD571 clearance, this does not negate the other teachings of Stephens that, in contrast to the placebo treatment, treatment with CDP571 anti-TNFα antibody had a dose-dependent effect on the treated patients, and all patients receiving anti-TNFα antibody scored a reduction in pain scale by week 1.

Thus, while Stephens teaches that under certain limited conditions (which fall within the scope of the instant claims but certainly do not fully encompass the scope of the instantly claimed method) the effectiveness of CDP571 anti-TNFα antibody would expected to be compromised, Stephen's nevertheless teaches that treatment of rheumatoid arthritis with 0.1 mg/kg CDP571 anti-TNFα antibody is effective.

Furthermore, the teachings of Salfeld provide a solution to the issue of CDP571 clearance that would be readily recognized by one of ordinary skill in the art.

In particular, one of ordinary skill in the art would have been motivated to substitute the human D2E7 antibody for the humanized CDP571 antibody because, as taught by Salfeld, a fully human antibody, such as D2E7, is preferable to a humanized antibody, such as CDP571, which is 95% human/5% murine, because while humanized antibodies are nearly identical to human antibodies, even a small amount of non-human sequence can elicit an unwanted immune reaction, especially so when administered for long periods as in the treatment of chronic rheumatoid arthritis (see Salfeld, paragraph bridging columns 1-2).

The Salfeld Reference

Applicant acknowledges Salfeld teaches an effective dose of anti-TNFα antibody is 0.1–20 mg/kg. However, applicant argues Salfeld fails to teach treatment with a dose of 0.01-0.1 mg/kg. Moreover, applicant argues that given the teachings of Salfeld that 0.1-20 mg/kg is an effective dose of anti-TNFα antibody, one of ordinary skill in the art would not have been motivated to use a dose of 0.01-0.1 mg/kg anti-TNFα antibody to treat rheumatoid arthritis. Applicant continues, "[f]urther, when considering prior art disclosing a range which "touches" the claimed range, "unexpected results [within the claimed narrow range] may.., render the claims unobvious" (see M.P.E.P. §2131.03). In the present case, while the Salfeld discloses a dose range which "touches" the claimed dose range of 0.01-0.1 mg/kg, the unexpected results provided by Applicants further prove that the pending claims are unobvious over the teachings of Salfeld.

Applicant's "unexpected result" is that mice transgenic for TNFα (tg197 mice), which is one model system for rheumatoid arthritis, can allegedly have their arthritis symptoms alleviated with 0.01 – 0.1 mg/kg anti-TNFα antibody. Therefore, applicant alleges human rheumatoid arthritis could also be treated with the same dose.

However, applicant has not established the closest prior art and compared it to their results to establish why their results were unexpected.

"A comparison of the *claimed* invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference." *In re Merchant*, 575 F.2d 865, 868, 197 USPQ 785, 787 (CCPA 1978) (emphasis in original). See MPEP § 716.02(e).

Nevertheless, assuming that den Broeder is the closest prior art, den Broeder teaches a dose titration clinical trial of the D2E7 anti-TNFα antibody in which rheumatoid arthritis patients were effectively treated with a dose of 0.25 mg/kg/2-4 weeks.

While den Broeder teaches their trial was not designed to include anti-TNFα antibody dose steps smaller than 0.25 mg/kg, den Broeder further teaches that the anti-TNFα antibody dosage could be even further reduced in light of the absence of any disease flare-ups in the patients treated with 0.25 mg/kg D2E7 every 2-4 weeks. Furthermore, den Broeder teaches that even lower dosages are "supported by the remarkably long duration of response seen in some patients after only one administration of anti-TNF-α antibody, documented for both D2E7 (up to 14 weeks EULAR response) and infliximab (up to approximately 18 weeks Paulus 20 response)." (see den Broeder, in particular Patients and Methods, Results and Discussion, pages 639-641, including 641 2nd paragraph).

Converting the 0.25 mg/kg/2-4 weeks dosage of den Broeder to a per week basis gives 0.0625 – 0.125 mg/kg/week, which overlaps the claimed dosage range of 0.01 to 0.1 mg/kg.

Thus, based on the teachings of den Broeder the ability to treat rheumatoid arthritis with a dose of 0.01 to 0.1 mg/kg anti-TNFα antibody was expected.

Indeed, treatment of rheumatoid arthritis patients via the claimed methods was entirely obvious when the teachings of Stephens, Salfeld and den Broeder are considered in combination.

The den Broeder reference

Applicant argues "It is inappropriate for the Examiner to extrapolate from [den Broeder] by calculating the dosage on a weekly basis so that it falls within the Applicants dose range of 0.01 to 1.0 mg/kg." However, applicant's argument is not found convincing because applicant does not provide sound scientific reasoning or objective evidence in support of their argument.

Applicant further argues (applicant's emphasis), "one of skill in the art would not have been motivated, based on the disclosure of den Broeder, to practice the claimed invention of treating arthritis at a low dose of 0.01-0.1 mg/kg. Notably, den Broeder teaches that "[a] drawback of step-down dose titration is the inevitable disease flare in the titration phase" and note that "eighteen out of 21 patients experienced a flair of the disease" (page 641, last paragraph; emphasis added). Indeed, three out of 21 patients reached the dose of 0.25 mg/kg, while the remaining 18 patients experienced a flair in disease at even higher doses. Thus, den Broeder teaches away from the claimed low dose of 0.01-0.1 mg/kg in that it teaches that even at a dose of 0.25 mg/kg (or greater), 18 out of the 21 patients treated experienced a flair in disease. One of ordinary skill in the art would not have been motivated nor have had a reasonable expectation of success, based on the disclosure of den Broeder, to treat with doses lower than 0.25 mg/kg, since only a small percentage of patients (i.e., 3 out of 21) were observed to reach the dose of 0.25 mg/kg before exhibiting a flare in disease."

Applicant's argument is not found convincing.

If the possibility of "disease flare" were such as strong demotivator then why would den Broeder or any other medical practitioner of ordinary skill in the art ever undertake a "step-down dose titration" study which entails the "inevitable disease flare"? The examiner submits that one of ordinary skill in the art was motivated to do so essentially for the reasons of record put forth in the Office Action of August 8, 2007, namely that given the teaching of den Broeder, one of ordinary skill in the art would have been motivated to treat rheumatoid arthritis with the lowest possible effective dose of anti-TNFα antibody in order to minimize the risk associated with TNFα suppression and treatment costs (which is also emphasized by den Broeder, see Introduction at page 638-639).

It is noted that the teachings of den Broeder regarding anti-TNFα antibody dose titration are consistent with the teachings of Salfeld that anti-TNFα antibody dosage concentration and frequency is a results effective variable that should be "adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions". Indeed, applicant's assertion at page 8, 1st paragraph of their remarks that "[e]ven if, *arguendo,* some testing would be required to determine if the dose is affective on a particular patient, such experimentation would certainly not be "undue" for a skilled artisan, since drug dosages have to be optimized for each patient regardless," is consistent with the idea that either 1. a treatment naïve arthritis patient will have to continue to suffer the symptoms of disease while their lowest effective anti-TNFα dose is determined by routine optimization or 2. an arthritis patient currently receiving a larger dose of anti-TNFα antibody will have to risk a disease flare in order to determine their lowest effective dose by routine optimization.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Accordingly, the instant claims are unpatentable over Stephens in view of Salfeld and den Broeder.

It is noted that the functional properties of the anti-TNFα antibody (e.g. as recited in claim 41) are physical properties of the D2E7 antibody taught by Salfeld et al. It is further noted that treatment of specific symptoms of rheumatoid arthritis (e.g. as recited in claim 43) would necessarily be treated when treating rheumatoid arthritis as taught by Salfeld et al.

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1–7, 17, 19, 20, 36-39, 49, 51, 52, 68, 69 and 70 of U.S. Patent No. 6,509,015 in view of Salfeld et al. (US Patent No. 6,258,562) and den Broeder (Rheumatology (Oxford). 2002 Jun;41(6):638-42).

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

As a preliminary matter, it is noted that the elected species of disease under examination is "rheumatoid arthritis"; however, certain claims of U.S. Patent No. 6,509,015 reading on other species of arthritic diseases are also included in this rejection because they anticipate the instant claims drawn to the a method of treating the genus of arthritic diseases.

The reference claims are directed to a method of treating various forms of arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. US Patent No. 6,258,562 clarifies, e.g. in columns 2-3 bridging paragraph, that the claimed methods employ antibody D2E7, i.e. the same antibody as recited in the instant claims.

Since treatment of the same disorder is claimed in U.S. Patent Nos. 6,509,015 and as in the instant application, i.e., rheumatoid arthritis, the symptoms of the disorder are inherently the same, and therefore are not patentably distinct from the instant claimed invention.

The instant claims differ from the reference teachings in the recitation of a "dose of 0.01 – 0.1 mg/kg."

However, as put forth in detail in the previous Office Actions of February 8, 2007 and August 8, 2007, and for the reasons put forth in the 35 U.S.C. § 102(b) and 103(a) rejections given above, the reference claims, in view of the teachings of Salfeld and den Broeder, render the claimed invention obvious.

11. Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 7,223,394 in view of Salfeld et al. (US Patent No. 6,258,562) and den Broeder (Rheumatology (Oxford). 2002 Jun;41(6):638-42).

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

As a preliminary matter, it is noted that the elected species of disease under examination is "rheumatoid arthritis"; however, certain claims of U.S. Patent No. 7,223,394, reading on other species of arthritic diseases are also included in this rejection because they anticipate the instant claims drawn to the a method of treating the genus of arthritic diseases.

Claims 1-10 of U.S. Patent No. 7,223,394 are directed to a method of treating rheumatoid arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. The reference specification clarifies that the claimed methods employ antibody D2E7, i.e. the same antibody as recited in the instant claims.

Since treatment of the same disorder is claimed in U.S. Patent No. 7,223,394 copending application USSN 11/233,252 as in the instant application, i.e., rheumatoid arthritis, the symptoms of the disorder are inherently the same, and therefore are not patentably distinct from the instant claimed invention.

The instant claims differ from the reference teachings in the recitation of a "dose of 0.01 – 0.1 mg/kg."

However, as put forth in detail in the previous Office Actions of February 8, 2007 and August 8, 2007, and for the reasons put forth in the 35 U.S.C. § 102(b) and 103(a) rejections given above, the reference claims, in view of the teachings of Salfeld and den Broeder, render the claimed invention obvious.

12. Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17, 41, 79, 86, 103, 110, 115, 122, 127 and 134 of USSN 11/233,252 in view of Salfeld et al. (US Patent No. 6,258,562) and den Broeder (Rheumatology (Oxford). 2002 Jun;41(6):638-42).

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 17, 41, 79, 86, 103, 110, 115, 122, 127 and 134 of USSN 11/233,252 are directed to a method of treating rheumatoid arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. The reference specification clarifies that the claimed methods employ antibody D2E7, i.e. the same antibody as recited in the instant claims.

Since treatment of the same disorder is claimed in copending application USSN 11/233,252 as in the instant application, i.e., rheumatoid arthritis, the symptoms of the disorder are

inherently the same, and therefore are not patentably distinct from the instant claimed invention.

The instant claims differ from the reference teachings in the recitation of a "dose of 0.01 – 0.1 mg/kg."

However, as put forth in detail in the previous Office Actions of February 8, 2007 and August 8, 2007, and for the reasons put forth in the 35 U.S.C. § 102(b) and 103(a) rejections given above, the reference claims, in view of the teachings of Salfeld and den Broeder, render the claimed invention obvious.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
February 26, 2008

/Michail A Belyavskyi/
Primary Examiner, Art Unit 1644